Complete Summary

GUIDELINE TITLE

Hemorrhagic fever viruses as biological weapons: medical and public health management.

BIBLIOGRAPHIC SOURCE(S)

Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, Ksiazek T, Johnson KM, Meyerhoff A, O'Toole T, Ascher MS, Bartlett J, Breman JG, Eitzen EM Jr, Hamburg M, Hauer J, Henderson DA, Johnson RT, Kwik G, Layton M, Lillibridge S, Nabel GJ, Osterholm MT, Perl TM, Russell P, Tonat K. Hemorrhagic fever viruses as biological weapons: medical and public health management. JAMA 2002 May 8;287(18):2391-405. [140 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Exposure to or infection with viral hemorrhagic fever (Filoviridae: Ebola and Marburg; Arenaviridae: Lassa fever and New World arenaviruses; Bunyaviridae: Rift Valley fever; Flaviviridae: Yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pathology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To develop consensus-based recommendations for measures to be taken by medical and public health professionals if hemorrhagic fever viruses are used as biological weapons against a civilian population

TARGET POPULATION

Civilian adults, pregnant women, and children exposed to or infected with a hemorrhagic fever virus that has been used as a biological weapon

INTERVENTIONS AND PRACTICES CONSIDERED

Key Medical and Public Health Interventions After Identification of Suspected Index Case of Viral Hemorrhagic Fever

Identification

Identify suspected index case using these clinical criteria:* temperature $\geq$101 degrees F (38.3 degrees C) of <3 weeks' duration; severe illness, and no predisposing factors for hemorrhagic manifestations; and at least 2 of the following hemorrhagic symptoms: hemorrhagic or purple rash, epistaxis, hematemesis, hemoptysis, blood in stools, other, and no established alternative diagnosis.

Reporting

1. Report immediately to local and/or state health department.
2. Report immediately to infection control professional and laboratory personnel.

Treatment

1. Initiate supportive and ribavirin therapy (see Table 4 in the original guideline document) immediately while diagnostic confirmation is pending.
2. If infection with arenavirus or bunyavirus is confirmed, continue 10-day course of ribavirin.
3. If infection with filovirus or flavivirus is confirmed, or if the diagnosis of viral hemorrhagic fever is excluded or an alternative diagnosis is established, discontinue ribavirin.

Infection Control Measures

1. Initiate viral hemorrhagic fever-specific barrier precautions.
2. Initiate airborne precautions, with negative-pressure rooms if resources are available.

Public Health Measures

1. Confirm or exclude diagnosis via Laboratory Response Network.
2. Designated public health authority begins epidemiologic investigation.
3. Identify close and high-risk contacts and place under medical surveillance for 21 days from day of suspected/known exposure.
4. If contact does not have temperature $\geq$101 degrees F (38.3 degrees C) or signs or symptoms of viral hemorrhagic fever by the end of 21 days, discontinue medical surveillance.
5. If contact has temperature $\geq$101 degrees F (38.3 degrees C) or signs or symptoms consistent with viral hemorrhagic fever, initiate diagnostic workup and treatment, infection control, and public health interventions described for index case.

[*] Criteria are adapted from the World Health Organization's surveillance standards for acute hemorrhagic fever syndrome.

MAJOR OUTCOMES CONSIDERED

Therapeutic efficacy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The developers searched MEDLINE databases for the period from January 1966 to January 2002 for the Medical Subject Headings: viral hemorrhagic fever, Ebola,

Marburg, Lassa, arenavirus, Junin, Guanarito, Machupo, Sabia, CCHF, Rift Valley fever, hantavirus, dengue, yellow fever, Omsk hemorrhagic fever, Kyasanur Forest disease, biological weapons, biological terrorism, biological warfare, and biowarfare. The references were reviewed and relevant materials published prior to 1966 were identified. The working group also identified other published and unpublished references for review.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Three formal drafts of the statement that synthesized information obtained in the evidence-gathering process were reviewed by the working group. Each draft incorporated comments and judgments of the members.

All members approved the final draft.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnosis

A high index of suspicion will be required to diagnose viral hemorrhagic fever (VHF) among persons exposed to a covert bioterrorist attack. In naturally occurring cases, patients are likely to have risk factors such as travel to Africa or Asia, handling of animal carcasses, contact with sick animals or people, or arthropod bites within 21 days of onset of symptoms. No such risk factors would be associated with a bioterrorist attack. The variable clinical presentation of these diseases presents a major diagnostic challenge. Clinical microbiology and public health laboratories are not currently equipped to make a rapid diagnosis of any of these viruses, and clinical specimens would need to be sent to the U.S. Centers for Disease Control and Prevention (CDC) or the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID; Frederick, MD), the only 2 level D laboratories in the Laboratory Response Network.

All suspected cases of hemorrhagic fever virus disease should be immediately reported to local and/or state health departments, who would then notify the Centers for Disease Control and Prevention. The World Health Organization (WHO)has developed surveillance standards for acute viral hemorrhagic fever syndrome with the aim of early detection of naturally occurring outbreaks and notification of cases, even before identification of the causal agent. This includes prompt reporting to public health authorities of any patient with acute onset of fever of less than 3 weeks' duration who is severely ill, has no known predisposing host factors for hemorrhagic manifestations, and has any 2 of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other hemorrhagic symptom. This broad definition may be useful in the early period following a confirmed bioterrorist-related case of viral hemorrhagic fever as well. Public health authorities may develop more specific case definitions after the etiologic agent is identified.

Public health authorities, in consultation with the Centers for Disease Control and Prevention, should provide assistance and detailed instructions to clinical laboratories and to clinicians for processing and transport of laboratory specimens required for diagnosis of these agents. (See the resource page titled "Packaging Protocols for Biological Agents/Diseases" at the Centers for Disease Control and Prevention Web site.)

Methods of diagnosis at specialized laboratories include antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody

detection by antibody-capture enzyme-linked immunosorbent assay, reverse transcriptase polymerase chain reaction (RT-PCR), and viral isolation. Antigen detection (by enzyme-linked immunosorbent assay) and reverse transcriptase polymerase chain reaction are the most useful diagnostic techniques in the acute clinical setting. Viral isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory. (A full description of biosafety level-4 criteria is available at the Centers for Disease Control and Prevention Web site.) There are only 2 biosafety level-4 facilities in the United States, located at the Centers for Disease Control and Prevention and the U.S. Army Medical Research Institute of Infectious Diseases, with in-depth diagnostic capability. Either the presence of IgM or a 4-fold rise in titer of IgG antibody between acute- and convalescent-phase serum samples are diagnostic of these viral illnesses, but antibody-capture enzyme-linked immunosorbent assay is of limited value in early diagnosis because antibodies to these viruses usually do not appear until onset of recovery, approximately at the second week of illness. The Centers for Disease Control and Prevention requires approximately 1 working day (with prior notification of arrival) to offer a preliminary laboratory diagnosis following receipt of patient specimens.

The diagnosis of viral hemorrhagic fever should be based initially on clinical criteria and judgment, with laboratory testing used to confirm or exclude this clinical diagnosis. Laboratory testing will require time and, in the event of a large attack, may be delayed or perhaps not possible given current laboratory capacities.

Treatment

The mainstay of treatment of viral hemorrhagic fever is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. Because in some cases intravenous fluids have not reversed hypotension and may have contributed to pulmonary edema, consideration should be given to early vasopressor support with hemodynamic monitoring. Mechanical ventilation, renal dialysis, and antiseizure therapy may be required. Intramuscular injections, aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulant therapies are contraindicated. Steroids are not indicated.

Therapy

There are no antiviral drugs approved by the U.S. Food and Drug Administration for treatment of hemorrhagic fever viruses. Ribavirin, a nucleoside analog, has some in vitro and in vivo activity against Arenaviridae and Bunyaviridae (including Crimean-Congo hemorrhagic fever) but no utility against Filoviridae or Flaviviridae. Oral ribavirin, in combination with interferon alfa, is Food and Drug Administration-approved for treatment of chronic hepatitis C virus infection. Intravenous ribavirin is of limited availability in the United States. It is produced by ICN Pharmaceuticals Inc (Costa Mesa, CA) for compassionate use under an investigational new drug (IND) application.

Recommendations for drug therapy by the working group are not approved by the U.S. Food and Drug Administration for any of these indications and should always be administered under an investigational new drug protocol. In a mass casualty situation, these requirements may need to be modified to permit timely administration of the drug. In addition, treatment of other suspected possible

causes, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of viral hemorrhagic fever.

In a contained casualty situation (in which a modest number of patients require therapy), the working group recommends that an intravenous regimen of ribavirin be given as described in Table 4 in the original guideline document, in accordance with Centers for Disease Control and Prevention's recommendations for treating patients with suspected viral hemorrhagic fever of unknown cause, pending identification of the agent. A similar dose has been used in the treatment of Lassa fever.

In a mass casualty situation (in which the number of persons requiring therapy is sufficiently high that delivery of intravenous therapy is no longer possible), an oral regimen of ribavirin as described in Table 4 in the original guideline document is recommended. This dose is currently licensed for treatment of chronic hepatitis C infection in the United States. Although it is substantially lower than that in the intravenous regimen, a similar dose has been used to treat a few patients with Lassa fever, and there are no available studies on tolerability or efficacy of higher doses of oral ribavirin.

Ribavirin is contraindicated in pregnancy. However, in the context of infection with viral hemorrhagic fever of unknown cause or secondary to an arenavirus or Rift Valley fever, the working group believes that the benefits appear likely to outweigh any fetal risk of ribavirin therapy, and ribavirin is therefore recommended. The associated mortality of viral hemorrhagic fever tends to be higher in pregnancy.

The use of oral or intravenous ribavirin is not approved by the Food and Drug Administration for children, and proper doses have not been established. Only aerosolized ribavirin has been approved by the Food and Drug Administration for children, to treat respiratory syncytial virus infection. However, in the context of infection with viral hemorrhagic fever of unknown cause or secondary to an arenavirus or Rift Valley fever, the working group believes that the benefits likely outweigh the risks of ribavirin therapy, and it is therefore recommended as described in Table 4 in the original guideline document. Similar doses have been used to treat children with adenovirus pneumonia and hepatitis C and were well tolerated. Ribavirin capsules may not be broken open and are only available in 200-mg doses. However, Schering-Plough Corp (Kenilworth, NJ) produces a pediatric syrup formulation (which is not commercially available) for use under an investigational new drug application.

For infections caused by filoviruses or flaviviruses, the working group recommends supportive medical care only. Ribavirin has been shown to have no clinical utility against these groups of viruses.

Passive Immunization

Studies and case reports evaluating convalescent plasma as therapy (or prophylaxis) of the diseases caused by hemorrhagic fever viruses have yielded mixed results depending on the disease, with some reports suggesting clinical utility and other studies showing no benefit. Passive immunization has also been associated with enhanced viral replication in experimentally infected animals. The logistics of collection, testing, and storing immune convalescent plasma are

formidable. In the United States, the paucity of survivors of these diseases and the lack of a national program that collects and stores hemorrhagic fever virus immune plasma preclude its use in the initial response to a bioterrorist attack. Development of methods to manufacture monoclonal antibodies and recent advances in selecting highly effective human-derived or humanized products may provide new approaches to therapy in the future.

Postexposure Prophylaxis

Effective prophylaxis following exposure to a hemorrhagic fever virus is hampered by the absence of effective vaccines and antiviral medications. The working group does not recommend preemptive administration of ribavirin in the absence of signs of infection to persons with known or suspected exposures to the hemorrhagic fever viruses. Ribavirin has no utility against filoviruses or flaviviruses. For arenaviruses, there is limited experimental evidence that postexposure prophylaxis with ribavirin will delay onset of disease but not prevent it. Furthermore, the effectiveness of ribavirin as postexposure prophylaxis for arenaviruses or Rift Valley fever virus has never been studied in humans. While 1995 Centers for Disease Control and Prevention guidelines (Update: management of patients with suspected viral hemorrhagic fever--United States. MMWR Morb Mortal Wkly Rep 1995 Jun 30;44:475-9) recommend ribavirin to high-risk contacts of patients with Lassa fever, a review and possible revision of these recommendations is to be shortly undertaken (James Hughes, MD, oral communication, January 10, 2002). However, public health professionals suggest that stratification of risk groups into high-risk and close contacts may facilitate counseling and outbreak investigation. High-risk contacts are those who have had mucous membrane contact with a patient (such as during kissing or sexual intercourse) or have had a percutaneous injury involving contact with the patient's secretions, excretions, or blood. Close contacts are those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with clinical evidence of viral hemorrhagic fever prior to initiation of appropriate precautions.

Persons considered potentially exposed to hemorrhagic fever viruses in a bioterrorist attack and all known high-risk and close contacts of patients diagnosed with viral hemorrhagic fever should be placed under medical surveillance. All such individuals should be instructed to record their temperatures twice daily and report any temperature of 101 degrees F (38.3 degrees C) or higher (or any symptom noted in Table 3 in the original guideline document) to a clinician, hospital epidemiologist, or public health authority designated with surveillance. Surveillance should be continued for 21 days after the person's deemed potential exposure or last contact with the ill patient.

If a temperature of 101 degrees F (38.3 degrees C) or higher develops, ribavirin therapy should be initiated promptly as presumptive treatment of viral hemorrhagic fever, as described in Table 4 in the original guideline document, unless an alternative diagnosis is established or the etiologic agent is known to be a filovirus or a flavivirus. In the case of close and high-risk contacts of patients diagnosed with Rift Valley fever or a flavivirus, only those who process laboratory specimens from a patient prior to initiation of appropriate precautions require medical surveillance, as these specific viruses are not transmitted from person to person but may be transmitted in the laboratory setting.

Vaccine

With the exception of yellow fever live attenuated 17D vaccine, which is highly effective when administered to travelers to endemic areas, there is no licensed vaccine for any of the hemorrhagic fever viruses. The yellow fever vaccine is produced in limited supply, and world stocks are not sufficient to meet a surge. This vaccine would not be useful in preventing disease if given in the postexposure setting because yellow fever has a short incubation period of 3 to 6 days, and neutralizing antibodies take longer to appear following vaccination.

Infection Control

Recommendations for Protective Measures Against Nosocomial Transmission of Hemorrhagic Fever Viruses

- Strict adherence to hand hygiene: Health care workers should clean their hands prior to donning personal protective equipment for patient contact. After patient contact, health care workers should remove gown, leg and shoe coverings, and gloves and immediately clean their hands. Hands should be clean prior to the removal of facial protective equipment (i.e., personal respirators, face shields, and goggles) to minimize exposure of mucous membranes with potentially contaminated hands, and once again after the removal of all personal protective equipment
- Double gloves
- Impermeable gowns
- N-95 masks or powered air-purifying respirators, and a negative isolation room with 6 to 12 air changes per hour, as required by Healthcare Infection Control Practices Advisory Committee (Centers for Disease Control and Prevention) standards for airborne precautions[*]
- Leg and shoe coverings
- Face shields[**]
- Goggles for eye protection[**]
- Restricted access of nonessential staff and visitors to patient's room
- Dedicated medical equipment, such as stethoscopes, glucose monitors, and, if available, point-of-care analyzers
- Environmental disinfection with an Environmental Protection Agency-registered hospital disinfectant or a 1:100 dilution of household bleach
- If there are multiple patients with viral hemorrhagic fever in one health care facility, they should be cared for in the same part of the hospital to minimize exposures to other patients and health care workers

[*] These resources may not be possible in many health care facilities or in a mass casualty situation. In this case, all other measures should be taken and would, in combination, be expected to substantially diminish the risk of nosocomial spread.

[**] Face shields and eye protection may be already incorporated in certain personal protective equipment, such as powered air-purifying respirators.

Given the lack of licensed or effective therapies and vaccines against the hemorrhagic fever viruses, efforts to prevent transmission of infection must rely on the meticulous implementation of and compliance with strict infection control measures. Filoviruses and arenaviruses are highly infectious after direct contact

with infected blood and bodily secretions. A suspected case of viral hemorrhagic fever must be immediately reported to the hospital epidemiologist (or infection control professional) and to the local or state health department. The epidemiologist (or infection control professional) should, in turn, notify the clinical laboratory (so that additional precautions are put in place) as well as other clinicians and public health authorities.

Isolation Precautions

Direct contact with infected blood and bodily fluids has accounted for the majority of person-to-person transmission of filoviruses and arenaviruses. Therefore, the guideline developers recommend that in the case of any patient with suspected or documented viral hemorrhagic fever, viral hemorrhagic fever-specific barrier precautions should be implemented immediately. These precautions do not reflect Healthcare Infection Control Practices Advisory Committee (Centers for Disease Control and Prevention) isolation guidelines terminology and are defined here as strict hand hygiene plus use of double gloves, impermeable gowns, face shields, eye protection, and leg and shoe coverings (given the copious amounts of infected material, such as vomitus and liquid stool, that may be present in the environment).

Airborne transmission of hemorrhagic fever viruses appears to be a rare event but cannot be conclusively excluded. Given the inability to completely exclude this potential, the lack of preventive vaccines, and, in the case of filoviruses, the lack of effective drug therapy, we recommend that in addition to viral hemorrhagic fever-specific barrier precautions, airborne precautions also be instituted. Airborne precautions entail the use of a high-efficiency particulate respirator for any person entering the room and, as required by Healthcare Infection Control Practices Advisory Committee (Centers for Disease Control and Prevention) standards, the patient should be placed in a room with negative air pressure, 6 to 12 air changes per hour, air exhausted directly to the outdoors or passage through a high-efficiency particulate air (HEPA) filter before recirculation, and doors kept closed. There are many circumstances in which the use of negative-pressure rooms may not be possible, including mass casualty situations. In such conditions, all other infection control measures should be taken (i.e., viral hemorrhagic fever-specific barrier precautions and a high-efficiency particulate air respirator for any person entering the room), which would, in combination, substantially reduce the risk of nosocomial transmission. Available evidence suggests that in the great preponderance of historical cases, these measures were sufficient to prevent transmission of disease to health care workers, family members, and other patients. Nonessential staff and visitors should have restricted access to patients' rooms. If there are multiple patients with viral hemorrhagic fever in a health care facility, they should be cared for in the same part of the hospital to minimize exposure to other persons.

All persons, including health care workers and laboratory personnel who have had a close or high-risk contact with a patient infected with a filovirus or an arenavirus within 21 days of the patient's onset of symptoms, prior to the institution of appropriate infection control precautions, should be placed under medical surveillance and managed as described in the section on postexposure prophylaxis. Laboratory personnel who have processed laboratory specimens from a patient with any hemorrhagic fever viruses (including Rift Valley fever and the

flaviviruses) within 21 days of the patient's onset of symptoms, prior to the institution of appropriate infection control precautions, should also be placed under medical surveillance.

Because some of these viruses may remain present in bodily fluids for long periods following clinical recovery, convalescent patients continue to pose a risk of disease transmission. Therefore, patients convalescing from a filoviral or an arenaviral infection should refrain from sexual activity for 3 months after clinical recovery.

Personal Protective Equipment

Powered air-purifying respirators (PAPRs) are theoretically more efficacious than N-95 disposable masks in providing respiratory protection from small-particle aerosols, mostly due to issues related to proper fitting of the masks. However, no data exist to support higher efficacy of powered air-purifying respirators over N-95 masks in preventing airborne transmission of infection in the health care setting. Powered air-purifying respirators are more expensive ($300-$600 vs less than $1 for disposable N-95 masks), are bulky, require maintenance, and impair voice communication to a higher degree than disposable N-95 masks. One study has shown that powered air-purifying respirators are associated with a higher incidence of needlestick injuries. Disadvantages of the N-95 masks include the difficulty in ensuring a reliable face-mask seal with each use and impossibility of effective use by bearded individuals. The theoretical advantage of powered air-purifying respirators over N-95 masks may be offset by the danger of increased needlestick or sharp injuries to those using powered air-purifying respirators in these settings. The N-95 masks (in combination with face shields and goggles) are likely equivalent in protection to powered air-purifying respirators in the health care setting.

Therefore, the developers recommend that clinicians caring for patients with a viral hemorrhagic fever use either N-95 masks or powered air-purifying respirators, depending on their familiarity with one or the other, the suitability for the individual, and availability at a given institution. Some experts have advocated that powered air-purifying respirators be used during cough-inducing procedures (i.e., endotracheal intubations, bronchoscopies), autopsies, and centrifugation or pipetting of laboratory specimens. While there are no data to support this recommendation, the guideline developers would concur as long as the health care workers are familiar with the use of powered air-purifying respirators and are not subjecting themselves to the risk of inadvertent needlestick injury.

Laboratory Testing

The hemorrhagic fever viruses described herein (including Rift Valley fever and the flaviviruses) are highly infectious in the laboratory setting and may be transmitted to laboratory personnel via small-particle aerosols. The risk is especially high during aerosol-generating procedures, such as centrifugation. To minimize the possibility of small-particle aerosol generation, all laboratory staff must be alerted to any suspected diagnosis of viral hemorrhagic fever. Designated laboratory workers should receive training in handling specimens from any suspected viral hemorrhagic fever patients in advance of such an event. Laboratory workers should wear personal protective equipment that ensures viral hemorrhagic fever-specific barrier and airborne precautions. All specimens should

be handled, at a minimum, in a class 2 biological safety cabinet following BSL-3 practices. (Detailed descriptions of class 2 biological safety cabinets and BSL-3 practices are available at the Centers for Disease Control and Prevention Web site.) Most clinical facilities are not equipped with a BSL-3 laboratory. Virus isolation should only be attempted in a BSL-4 laboratory.

Potential hazards associated with handling of clinical specimens from patients infected with a hemorrhagic fever virus pose great problems in hospital facilities. Laboratory tests should be limited to critical diagnostic tests. If adequate resources are available, point-of-care analyzers for routine laboratory analysis of infected patients should be used. Point-of-care analyzers are small, portable devices that may be used at the bedside, require only a few drops of fresh whole blood, display test results in a few minutes, limit the exposure of laboratory personnel to infectious clinical specimens, do not disrupt the clinical laboratory routine, and do not contaminate clinical laboratory equipment.

If point-of-care analyzers are not available, clinical specimens need to be processed in a clinical laboratory. Precautions that parallel those of a U.S. hospital's successful efforts to care for a patient infected with a New World arenavirus should be followed. Laboratory specimens should be clearly identified, double bagged, and hand carried to the laboratory at prescheduled times, preferably prior to equipment maintenance to enable decontamination of instruments after testing. Specimens should never be transported in pneumatic tube systems. Only dedicated, trained laboratory personnel should process clinical specimens from patients with viral hemorrhagic fever, wearing protective equipment to ensure airborne and viral hemorrhagic fever-specific barrier precautions. Serum should be pretreated with the detergent Triton X-100 (10 microliters of 10% Triton X-100 per 1 mL of serum for 1 hour). Pretreatment with Triton X-100 may reduce the titers of these enveloped viruses, but efficacy has not been tested. Pretreatment with Triton X-100 does not significantly alter serum electrolytes, urea nitrogen, creatinine, and glucose or liver function test results. Additional guidelines for clinical specimen transport, processing, and disposal have been described by Armstrong et al (Armstrong LR, Dembry LM, Rainey PM, et al. Management of a Sabia virus-infected patients in a US hospital. Infect Control Hosp Epidemiol 1999;20:176-82).

Postmortem Practices

In the event of an outbreak of viral hemorrhagic fever, special provisions will be required for burial practices. Contact with cadavers has been implicated as a source of transmission in the Kikwit Ebola outbreak of 1995 and in Uganda in 2000. The guideline developers recommend that trained personnel, using the same infection control precautions as those used to transport ill patients, handle the bodies of patients who die of viral hemorrhagic fever. Autopsies should be performed only by specially trained persons using viral hemorrhagic fever-specific barrier precautions and high-efficiency particulate air-filtered respirators (N-95 masks or powered air-purifying respirators) and negative-pressure rooms, as would be customary in cases in which contagious biological aerosols, such as Mycobacterium tuberculosis, are deemed a possible risk. The guideline developers recommend prompt burial or cremation of the deceased, with minimal handling. Specifically, no embalming should be done. Surgery or postmortem examinations are associated with increased risks of transmission and should be done only when absolutely indicated and after consultation with experts.

Environmental Decontamination

Linen handlers and workers involved in environmental decontamination should wear personal protective equipment that ensures viral hemorrhagic fever-specific barrier precautions. The guideline developers recommend that contaminated linens be placed in double bags and washed without sorting in a normal hot water cycle with bleach. Alternatively, they may be autoclaved or incinerated. Detailed instructions on handling and disinfection of contaminated linens are available from the Centers for Disease Control and Prevention (Update: management of patients with suspected viral hemorrhagic fever--United States. MMWR Morb Mortal Wkly Rep 1995 Jun 30;44:475-9). Environmental surfaces in patients' rooms and contaminated medical equipment should be disinfected with an Environmental Protection Agency–registered hospital disinfectant or a 1:100 dilution of household bleach.

It has been suggested that excreta should be disinfected with 0.6% sodium hypochlorite before disposal. Although a theoretical concern remains that the disposal of contaminated human excreta may contaminate sewage systems, the working group does not recommend the addition of disinfectants to human excreta prior to disposal. Disinfectants are not effective in sterilizing solid waste, the indiscriminate addition of hypochlorite may damage septic tanks, and these viruses are not likely to survive standard sewage treatment in the United States.

In general, in their natural state, these lipid-enveloped viruses are not environmentally stable and are not expected to persist in the environment for prolonged periods. Decisions regarding the need for and methods of decontamination following an attack with a hemorrhagic fever virus should be made following expert analysis of the contaminated environment and the weapons used in the attack, in consultation with experts in environmental remediation.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Clinical and epidemiological data are limited; outbreaks are sporadic and unanticipated, and there are few case series or clinical trials involving human subjects.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate identification, diagnosis, treatment and containment of hemorrhagic fever viruses following a bioterrorist attack.

POTENTIAL HARMS

Ribavirin. Although a risk of human teratogenicity has not been demonstrated for ribavirin, its pharmacologic action and its teratogenicity and embryolethality in several animal species raise concern that such a risk may exist with maternal therapy during pregnancy. Therefore, ribavirin is classified as a pregnancy category X drug, and is contraindicated in pregnancy. The primary adverse effect caused by ribavirin is a dose-related, reversible, hemolytic anemia. However, a range of cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with combination ribavirin-interferon therapy for hepatitis C.

Ribavirin is contraindicated in pregnancy. However, in the context of infection with viral hemorrhagic fever of unknown cause or secondary to an arenavirus or Rift Valley fever, the working group believes that the benefits appear likely to outweigh any fetal risk of ribavirin therapy, and ribavirin is therefore recommended. The associated mortality of viral hemorrhagic fever tends to be higher in pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The views, opinions, assertions, and findings contained herein are those of the guideline authors and should not be construed as official U.S. Department of Health and Human Services, U.S. Department of Defense, or U.S. Department of Army positions, policies, or decisions unless so designated by other documentation. The recommendations on the use of drugs for uses not approved by the U.S. Food and Drug Administration (FDA) do not represent the official views of the U.S. Food and Drug Administration or of any of the U.S. federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.
- Several viruses that can cause viral hemorrhagic fever were not considered in this guideline. Dengue was excluded because it is not transmissible by small-particle aerosol, and primary dengue causes viral hemorrhagic fever only rarely. Crimean-Congo hemorrhagic fever (CCHF) and the agents of hemorrhagic fever with renal syndrome (HFRS) were also excluded after much deliberation. Although these pathogens can cause viral hemorrhagic fever and may be transmissible by small-particle aerosol, the working group noted that technical difficulties (i.e., barriers to large-scale production) currently preclude their development as mass casualty weapons. Crimean-Congo hemorrhagic fever and the agents of hemorrhagic fever with renal syndrome do not readily replicate to high concentrations in cell cultures, a prerequisite for weaponization of an infectious organism. However, Crimean-Congo hemorrhagic fever, the agents of hemorrhagic fever with renal syndrome, and dengue may carry great morbidity and mortality in naturally occurring outbreaks. In particular, Crimean-Congo hemorrhagic fever may be transmitted from person to person, has a high case-fatality rate, and is endemic in central Asia and southern Africa. The guideline developers acknowledge that technical difficulties may be overcome with advances in technology and science, and these excluded viruses may become a greater threat in the future. The guideline developers provide references to other

sources providing information on the viruses not addressed within the guideline (refer to the original guideline document).
- The consequences of an unannounced aerosol attack with a hemorrhagic fever virus are the primary focus of the analysis. A variety of attack scenarios with these agents are possible. The analysis does not attempt to forecast the most likely but focuses on perhaps the most serious scenario. Understanding and planning for a covert aerosol attack with hemorrhagic fever viruses will improve preparedness for other scenarios as well.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 May 8

GUIDELINE DEVELOPER(S)

Center for Biosecurity - Academic Institution

GUIDELINE DEVELOPER COMMENT

The Working Group on Civilian Biodefense included 26 representatives from academic medical centers, public health, military services, governmental agencies, and other emergency management institutions, including:

- The Center for Civilian Biodefense Strategies and the Departments of Microbiology and Neuroscience, School of Medicine, Johns Hopkins University, and Division of Infectious Diseases, Johns Hopkins School of Medicine
- Critical Care Medicine Department, Clinical Center, Fogarty International Center, and Vaccine Research Center, National Institutes of Health
- Center for Biodefense, University of Texas Medical Branch
- U.S. Army Medical Research Institute of Infectious Diseases
- National Center for Infectious Diseases, Centers for Disease Control and Prevention
- Departments of Biology and Medicine, University of New Mexico
- Office of the Commissioner, U.S. Food and Drug Administration
- Office of Emergency Preparedness, Department of Health and Human Services
- Office of Public Health Preparedness, Department of Health and Human Services
- Nuclear Threat Initiative
- Bureau of Communicable Diseases, New York City Health Department
- Center for Infectious Disease Research and Policy, University of Minnesota

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Not stated

GUIDELINE COMMITTEE

Working Group on Civilian Biodefense

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The Working Group on Civilian Biodefense included 26 representatives from academic medical centers, public health, military services, governmental agencies, and other emergency management institutions.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Journal of the American Medical Association (JAMA) Web site.

Full text available in:

- HTML Format
- Portable Document Format (PDF)

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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